EPA MUNCHEN

PATENT COOPERATION TREATY

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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ACTION

Att.; Dr J. Claire Irvine

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	03.08.2000
Applicant's or agent's file reference: N.78459DMG/TJD	REPLY DUE: within 1 month(s) from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/09346	30/04/1999	01/05/1998

International Patent Classification (IPC) or both national classification and IPC
C12N15/31

Applicant
CHIRON CORPORATION et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☒	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☒	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain document cited
VII	☒	Certain defects in the international application
VIII	☒	Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 01/09/2000.

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WRITTEN OPINION

International application No. PCT/US99/09346

I. Basis of the opinion

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*):

Description, pages:

1-1419 as originally filed

Claims, No.:

1-18 as originally filed

Drawings, sheets:

1/31-31/31 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

II. Priority

1. ☒ This opinion has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

   ☒ copy of the earlier application whose priority has been claimed.

   ☐ translation of the earlier application whose priority has been claimed.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this opinion, th international filing date indicated above is considered to be the relevant date.

WRITTEN OPINION International application No. PCT/US99/09346

3. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 1, 3, 16, 18 (completely); 2, 4-15, 17 (partially),

because:

☒ the said international application, or the said claims Nos. 1, 3, 16, 18 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 2, 4-15, 17 (partially).

IV. Lack of unity of invention

1. In response to the invitation (Form PCT/IPEA/405) to restrict or pay additional fees, the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with for the following reasons and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees:

3. Consequently, the following parts of the international application were the subject of international preliminary

examination in establishing this opinion:

☐ all parts.

☒ the parts relating to claims Nos. 2, 4-15, 17 (partially).

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	5, 8, 11-15 (partially) NO
Inventive step (IS)	Claims	5, 8, 11-15 (partially) NO
Industrial applicability (IA)	Claims	-

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

WRITTEN OPINION
SEPARATE SHEET

International application No. PCT/US99/09346

Re Item II

Priority

The right of priority was not assessed because the priority document is missing.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The applicant failed to pay additional examination fees and requested in his letter of 21.07.00 that the International Preliminary Examination Report be established on the basis of Invention 5 (SEQ ID No: 1201/1202).
Consequently, claims 2, 4-15 and 17 were examined as far as these claims concern SEQ ID No. 1201/1202.
Claims 1, 3, 16 and 18 were disregarded.

Re Item IV

Lack of unity of invention

The objection for lack of unity raised by the International Search authority is maintained by the International Examination Authority. The International Search Authority found this application to contain 1510 different inventions. Search fees were paid for 8 inventions. Thus, the current application concerns 8 different inventions:

Invention 1 (claims 1, 3, 16, 18, all completely; 2, 4-15, 17, all partially)
A protein comprising the amino acid sequence of SEQ ID NO: 2790 or comprising a fragment of at least 7 (preferably consecutive) amino acids of said SEQ ID NO; a protein having 50% or greater homology to said protein(s); an antibody binding to said protein(s); a nucleic acid encoding said protein(s), preferably comprising the nucleotide sequence of SEQ ID NO: 2789 or a fragment comprising 10 or more consecutive nucleotides thereof; complementary nucleic acid molecules; compositions comprising said protein(s), nucleic acid(s) or antibody for vaccination, diagnosis or pharmaceutical use, preferably immunogenic compositions comprising said protein(s), and the use of said composition(s).

Invention 2 (claims 2, 4-15, 17, all partially)
A protein comprising the amino acid sequence of SEQ ID NO: 2 or comprising a fragment of at least 7 consecutive amino acids of said SEQ ID NO; an antibody binding to said protein(s); a nucleic acid encoding said protein(s), preferably comprising the nucl-otid-

sequence of SEQ ID NO: 1 or a fragment comprising 10 or more consecutive nucleotides thereof; complementary nucleic acid molecules; compositions comprising said protein(s), nucleic acid(s) or antibody for vaccination, diagnosis or pharmaceutical use, preferably immunogenic compositions comprising said protein(s), and the use of said composition(s).

invention 3 (claims 2, 4-15, 17, all partially)
As invention 2 but concerning SEQ ID NO: 441/442, respectively.

Invention 4 (claims 2, 4-15, 17, all partially)
As invention 2 but concerning SEQ ID NO: 489/490, respectively.

Invention 5 (claims 2, 4-15, 17, all partially)
As invention 2 but concerning SEQ ID NO: 1201/1202, respectively.

Invention 6 (claims 2, 4-15, 17, all partially)
As invention 2 but concerning SEQ ID NO: 1455/1456, respectively.

invention 7 (claims 2, 4-15, 17, all partially)
As invention 2 but concerning SEQ ID NO: 1745/1746, respectively.

invention 8 (claims 2, 4-15, 17, all partially)
As invention 2 but concerning SEQ ID NO: 2791/2792, respectively.

Only Invention 5 (SEQ ID No.: 1201/1202) was examined (see Item III)

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: ROKBI B ET AL.: 'Evaluation of recombinant transferrin - binding protein B variants from Neisseria meningitidis for their ability to induce cross-reactive and bactericidal antibodies against a genetically diverse collection of serogroup B strains.' INFECTION AND IMMUNITY, vol. 65, no. 1, January 1997 (1997-01), pages 55-63, XP002138643

D2: DATABASE GCG_GENESEQ [Online] ID W14640, AC W14640, 5 March 1998

WRITTEN OPINION
SEPARATE SHEET

International application No. PCT/US99/09346

(1998-03-05) QUENTIN-MILLET M J ET AL.: 'N. meningitidis HTR Tbp2 (del377-385, del407-465, del488-508)' XP002138654 -& WO 97 13860 A (PASTEUR MERIEUX SERUMS VACC; QUENTIN MILLET MARIE JOSE (FR); ROKBI)) 17 April 1997 (1997-04-17)

Novelty (Art. 33(2) PCT)
Document D1 discloses recombinant transferrin binding proteins (Tbp) from Neisseria meningitidis capable of inducing cross-reactive and bactericidal antibodies against various serogroup B neisseria species.
Document D2 discloses the sequence of a Tbp protein having 23,5% identity to SEQ ID No.: 1202 of the present application.
It thus cannot be excluded that the antibodies disclosed in document D1 may cross-react with the protein of SEQ ID no.: 1202. Consequently, the subject-matter of claim 5 is not novel.

Concerning claim 8, the Applicant's attention is drawn to the fact that 10 nucleotides encode 3 amino acids (and not 7, as claimed in claim 4). Document D2 discloses streches of amino acid sequences of at least 3 amino consecutive amino acids which can be found in SEQ ID No.: 1202. Therefore, it cannot be excluded that similar short fragments of DNA may be comprised by the sequence disclosed in D2. Moreover, in D2, DNA fragments are contemplated which encode polypeptides of at least 10 amino acids, said polypeptides having at least 70% homology with the sequence claimed in D2 (see e.g. pages 16-17). Such homologies are already observed between SEQ ID No.: 1202 (e.g. positions 429-441) and the sequence claimed in D2 (positions 496-508). Thus, the nucleic acid fragments of claim 8 are embodiments of the fragments contemplated in D2. Consequently, claims 8, 11, 12-15 lack novelty.

The Applicant's attention is drawn to the fact that the intention of use does not limit the scope of a claim which is directed to a composition. The claim must be interpreted as being directed to a composition per se regardless of its use. No unified criteria exist in the PCT as far as first medical use is concerned. The EPO, for instance, will allow claims in a form such as:"substance or composition X", followed by the indication of use ("for use as a medicament").
Thus, claims 12-15 are directed to compositions comprising the antibody of claim 5. Such compositions are disclosed for use as a pharmaceutical in the treatment of Neisseria

WRITTEN OPINION
SEPARATE SHEET

International application No. PCT/US99/09346

infections or prevention in D1/D2. Consequently, claims 12-15 are not novel.

To summarize, claims 5, 8, 11-15 are not novel and thus, neither inventive.

Inventive step (Art. 33(3) PCT)
Document D2 can be considered as the closest prior art since it concerns a protein from Neisseria meningitidis useful as immunogenic component of broad spectrum vaccines. The problem underlying the current application is the provision of alternative sequences of proteins useful as antigens for the generation of antibodies. The solution provided by the present application is the provision of nucleic acid and protein of SEQ ID No.: 1201/1202. However, none of the documents cited in the International Search Report would have allowed the skilled person to achieve said subject-matter (full length sequence) in an obvious manner. Therefore, inventive step could be acknowledged for this novel Neisseria meningitidis antigen.
Concerning claims 4 (see e.g. homology at positions 20-25 of SEQ ID No.: 1202 with D2 sequence at positions 3-8), 8 and 11, the Applicant's attention is drawn to the fact that, conservative changes or addition of one or two amino acids to the sequence of the claimed fragments without achieving an advantageous technical effect, even if these fragments are then novel, will not establish a basis for inventive activity.

Re Item VII

Certain defects in the international application

The following back references were read as bellow:
In claim 7 to claim 6 instead of claim 5
In claim 9 to claim 6 instead of claim 5
In claim 10 to claim 7 instead of claim 6
In claim 11 to claim 7 instead of claim 8
In claim 13, 14 and 15 to claim 12 instead of claim 11.

Re Item VIII

Certain observations on the international application

1. Clarity (Art. 6 PCT)
   Claim 17 is read as being directed to a composition per se comprising the product of claim 2, and thus, being equivalent to claim 12 as far as the latter concerns the protein of claim 2.

WRITTEN OPINION
SEPARATE SHEET

International application No. PCT/US99/09346

2. Support by specification (Art. 6 PCT) in combination with Art. 5 PCT (complete and enabling disclosure)
There seems to be no experiments which provide evidence that the specific protein, antibodies or nucleic acid could be successfully used as a medicament or pharmaceutical. All evidence provided was in vitro (e.g. Fig 8). Therefore, claims 13-15 are not supported by the specification.